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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,099	01/20/2004	Timothy J. O'Leary	AFIP 03-16 01	4916

27370 7590 10/12/2007

OFFICE OF THE STAFF JUDGE ADVOCATE
U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
ATTN: MCMR-JA (MS. ELIZABETH ARWINE)
504 SCOTT STREET
FORT DETRICK, MD 21702-5012

EXAMINER	
CALAMITA, HEATHER	
ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
10/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,099	O'LEARY ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on August 3, 2007, has been entered.

Status of Application, Amendments, and/or Claims

2. Amendments of August 6, 2007, have been received and entered in full. Claims 16-43 are pending and under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16, 17, 20-28, 32-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) in view of Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS).

With regard to claims 16 and 43, Singh et al. teach a method for immunoliposome assay comprising

a) encapsulating markers within the closed shell liposomal bilayers (see p. 6020 col. 1 lines 16-18 and p. 6021 Figure 2, where the term "closed shell" is not defined in the instant specification therefore the liposomal bilayer of Singh et al. is interpreted to meet this recitation)

b) associating receptors to the extravesicular surface of the liposomal bilayers (see p. 6020 col. 1 lines 8-14 and p. 6021 Figure 2)

c) exposing the selected receptors to an immobilized target analyte which bind to the liposomal bilayer associated selected receptors (see p. 6021 Figure 2, where the target analyte is the toxin)

d) removing unbound liposomal bilayers (see p. 6022 col. 1 under *Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins*, lines 14-18)

e) lysing the bound liposomal bilayers to release the markers (see p. 6022 col. 1 under *Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins*, lines 18-20)

g) detecting the markers (see p. 6022 col. 1 under *Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins*, lines 20-23).

With regard to claim 17, Singh et al. teach the analyte is a biological toxin (see p. 6022 col. 1 under *Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins*, lines 1-7)

With regard to claim 20, Singh et al. teach the receptors are gangliosides (see p. 6020 col. 1 lines 8-14 and p. 6021 Figure 2).

With regard to claims 21-23, Singh et al. teach liposomes provide sites for covalent attachment (see p. 6024 under *Conclusions*. Additionally, the covalent attachment of proteins (and antibodies) to hydrocarbons is well known in the art and within the ability of a skilled artisan to perform).

With regard to claims 24 and 25, Singh et al. teach associating receptors to the extravesicular surface of the liposomal bilayers comprises electrostatically coupling charged receptors to charged lipids in the liposomal bilayers (see p. 6023 under *Nonspecific Binding of*

Liposomes, where Singh teaches receptors (ie proteins) can adsorb to liposomes via electrostatic attraction).

With regard to claim 26, Singh et al. teach anchoring integral membrane protein receptors to the liposomal bilayers by direct incorporation into the liposomal bilayer (see p. 6020 col. 1 lines 8-14 and p. 6021 Figure 2).

With regard to claim 27, Singh et al. teach reducing non-specific binding of the liposomal bilayers on an immobilizing substrate by varying the lipid composition of the lipid bilayer to alter the size of the liposome, the fluidity of the bilayer or the polarity and charge of the surface of the bilayer (see p. 6023 under *Nonspecific Binding of Liposomes*, where Singh teaches liposomes, depending on their composition and groups present on the outer surface can exhibit non-specific binding).

With regard to claim 28, Singh et al. teach reducing non-specific binding of the liposomal bilayers on an immobilizing substrate by altering the charge density of the surface of the bilayer (see p. 6023 col. 2, where Singh teaches the use of BSA and polystyrene and negatively charged liposomes to reduce non-specific binding).

With regard to claim 32, Singh et al. teach the liposomal bilayers are lysed with Triton X-100 (see p. 6022 col. 1 under *Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins*, lines 1-7).

With regard to claims 39-41, Singh et al. teach detecting toxins in food (see p. 6024 col. 2, under *Conclusions*, where food monitoring and clinical diagnostics are disclosed).

With regard 42, Singh et al. teach the immobilized target analyte is immobilized on a microtiter plate (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-7).

Singh et al. do not teach all of the limitations of the claims, specifically with regard to claims 16 and 43, Singh do not teach step a) encapsulating a plurality of identical nucleic

acidsegments within the liposome step f) subsequently amplifying the nucleic acid segments and step g) detecting the released nucleic acids.

With regard to claim 19, Singh et al. do not teach teach using nucleic acids as reporters and amplifying the nucleic acid reporters using PCR, where the nucleic acids comprise 50-1000 identical nucleic acid segments).

With regard to claim 34, Singh et al. do not teach detecting with gel electrophoresis.

With regard to claim 33, Singh et al. do not teach the nucleic acid segments are amplicons that are amplified using PCR.

With regard to claim 35, Sing et al. do not teach the amplifying and detecting are coupled.

With regard to claim 36, Singh et al. do not teach detecting 10-1000 molecules of the analyte.

With regard to claim 37, Singh et al. do not teach detecting the analyte at subattomolar quantities.

With regard to claims 16 and 43 step a), Wu et al. teach using nucleic acids as reporters for amplification, f) amplifying the nucleic acids and g) detecting the nucleic acids as an indication of the presence of the analyte (see p. 322 col. 2 under Immuno-PCR assay lines 9-28 and p. 323 Figure 1).

With regard to claim 19, Wu et al. teach using nucleic acids as reporters and amplifying the nucleic acid reporters using PCR, where the nucleic acids comprise 50-1000 identical nucleic acid segments (see p. 322 col. 2 under Immuno-PCR assay lines 9-28, once the reporter is amplified there will be greater than 1000 nucleic acid segments).

With regard to claim 33, Wu et al. teach the nucleic acids are amplified using PCR (see p. 322 col. 2 under Immuno-PCR assay lines 9-28).

With regard to claim 34, Wu teaches detecting with gel electrophoresis (see p. 322 col. 2 under *Immuno-PCR assay*).

With regard to claim 35, Wu et al. teach the amplifying and the detecting are coupled (see p. 322 col. 2 under *Immuno-PCR assay*, where amplification occurred and the products were detected by gel electrophoresis).

With regard to claim 36, Wu teaches detecting 10-1000 molecules of the analyte (see the abstract)

With regard to claim 37, Wu teaches detecting the analyte at subattomolar quantities (see the abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods. Wu et al. state, "...the method described here demonstrates that immuno-PCR technology greatly extends the sensitivity of immunoassays. This hybrid technology exhibited analyte detection from 100 to 1000 fold better than the ELISA method performed with the same antibodies. Immuno-PCR technology, in principle, provides the basis for a new generation of sensitive immunoassays and may be useful in clinicopathological assays as well as detection of low level antigens (see p. 325 col. 1 first full paragraph)." An ordinary practitioner would have been motivated to substitute the markers in the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to improve the sensitivity of the immunoliposome assay. The DNA reporters disclosed by Wu enable detection of analytes present in a sample at very low levels because the DNA markers improve sensitivity from 100 fold to 1000 fold over standard immunoassay methods, therefore the ordinary practitioner would

expect a markedly higher degree of sensitivity in the immunoassay if the traditional fluorescence markers were substituted with the DNA reporters.

4. Claims 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) and Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS) in further view of Cao et al. (The Lancet, 2000).

The teachings and suggestions of Singh et al. and Wu et al. are described previously.

Singh et al. and Wu et al. do not teach or suggest all the limitations of claim 18.

With regard to claim 18, Cao teach the use of an assay (immuno PCR) to spatially localize an analyte within a fixed tissue section (see the abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods. Wu et al. state, "...the method described here demonstrates that immuno-PCR technology greatly extends the sensitivity of immunoassays. This hybrid technology exhibited analyte detection from 100 to 1000 fold better than the ELISA method performed with the same antibodies. Immuno-PCR technology, in principle, provides the basis for a new generation of sensitive immunoassays and may be useful in clinicopathological assays as well as detection of low level antigens (see p. 325 col. 1 first full paragraph)." An ordinary practitioner would have been motivated to substitute the markers in the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to improve the sensitivity of the immunoliposome assay. The DNA reporters disclosed by Wu enable detection of analytes present in a sample at very low levels because the DNA markers improve sensitivity from 100 fold to 1000 fold over standard immunoassay methods, therefore the ordinary practitioner would

expect a markedly higher degree of sensitivity in the immunoassay if the traditional fluorescence markers were substituted with the DNA reporters. It would have been further obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. and apply the method to in situ detection as taught by Cao in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods in a fixed tissue sample. Cao teaches a technique which uses the amplification of DNA markers is useful in situ because it allows for the detection of antigens or target analytes at low levels in in-tact cells or tissue sections (see p. 1002 paragraph bridging col. 1 and 2). A skilled artisan would recognize the advantage of using the immunoliposome assay method of Singh with the DNA markers of Wu and applying the method to in situ analysis in order to detectof antigens or target analytes at low levels in in-tact cells or tissue sections.

5. Claims 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) and Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS) in view of Boxer et al. (USPN 6,503,452 B1).

The teachings and suggestions of Singh et al. and Wu et al. are described previously.

Singh et al. and Wu et al. do not teach or suggest all the limitations of claims 29-30.

With regard to claims 29-30, Boxer et al. teach reducing non-specific binding by varying the spacer arm (see col. 14, line 8-12, where the spacer arm is polyethylene glycol).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. and Wu et al. with the PEG arm, as taught by Boxer et al. in order to immobilize the liposome while reducing non-specific binding. Boxer et al. teaches that a PEG spacer arm is an acceptable way to immobilize liposomes. An ordinary practitioner would have been motivated to use the

immunoliposome assay as taught by Singh et al. and Wu et al. with the PEG arm, as taught by Boxer et al. in order to successfully immobilize the liposome and reduce non-specific binding.

6. Claim 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) and Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS) in view of in view of Huang et al. (Biotechniques, 1996).

The teachings and suggestions of Singh et al. and Wu et al. are described previously.

Singh et al. and Wu et al. do not teach or suggest all the limitations of claims 31.

Huang et al. teach removal of contaminating DNA with DNase (see the abstract)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. and Wu et al. with DNase for the removal of contaminating DNA, as taught by Huang et al. in order to remove any contaminating DNA which could result in inaccurate results. Huang et al. teaches that DNase removes contaminating DNA (see abstract). An ordinary practitioner would have been motivated to use the immunoliposome assay as taught by Singh et al. and Wu et al. DNase, as taught by Huang et al. in order to successfully remove contaminating DNA from the assay and achieve more accurate results.

Response to Arguments

7. Applicants' arguments filed August 6, 2007, have been fully considered but they are not persuasive. With respect to the 103 (a) rejections over the cancelled claims, Applicants arguments are not persuasive to the extent the arguments apply to the new rejections. Applicants argue beginning on p. 9 of the response, Singh does not teach or suggest encapsulation of nucleic acid segments. This argument is not persuasive because Singh is not relied on for the teaching of encapsulating nucleic acid segments. Singh is relied on for the teaching of encapsulating a

marker specifically rhodamine for use in an immunoassay. Singh teaches using the Rhodamine marker of the liposomes to detect the presence of biological toxins. Singh teaches liposomes which have gangliosides (toxin receptors) integrated into the lipids of the liposomes. When the receptors are contacted with the toxin this interaction is detected via the rhodamine marker. Wu is relied on for the teaching of the nucleic acid segments (ie nucleic acid markers). Wu teaches the technique of Immuno-PCR which allows for the detection of analytes at very low concentrations because the DNA acts as a marker and when the analyte is present the DNA marker is amplified and detected. Applicant, argues that Wu does not overcome the deficiencies of Singh because Wu teach the reporter DNA is covalently linked to antibodies through amine and sulphhydryl groups and the combination of Singh and Wu would result in not only the encapsulation of the DNA reporters but also the antibodies. This argument is not persuasive because the combination of Wu and Singh is merely a substitution of one marker (the rhodamine marker of Singh) for another more sensitive marker (the DNA marker of Wu).

In the instant case, it well within the common knowledge and understanding of the skilled artisan that it would be advantageous to substitute DNA markers for Rhodamine markers in order to exploit the amplification properties of DNA and improve the sensitivity of the detection assay which employs DNA markers. Additionally it is within the understanding of a skilled artisan that DNA can be encapsulated in a liposome without being covalently attached to antibodies and still retain its amplifiable properties. A skilled artisan would in view of Wu substitute DNA markers for the Rhodamine marker of Singh in order to exploit the amplification properties of DNA and increases the sensitivity of the detection assay.

Additionally, the federal circuit held in *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, __ F.3d __ (Fed. Cir. 2007) a treatment method to be obvious citing the following:

1) *KSR* followed - Confirmation of Stem Cell Properties Obvious: The invention was novel in the sense that it was not confirmed in the prior art that umbilical cord blood is capable of hematopoietic reconstitution. Relying upon *KSR*, the court majority stated that "[w]hile the inventors may have proved conclusively what was strongly suspected before - that umbilical cord

blood is capable of hematopoietic reconstitution - and while their work may have significantly advanced the state of the science of hematopoietic transplantations by eliminating any doubt as to the presence of stem cells in cord blood, the mouse experiments and the conclusions drawn from them were not inventive in nature. Instead, the inventors merely used routine research methods to prove what was already believed to be the case. Scientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention."

For the instant case, it is clear that this situation applies here. The inventors proved what was strongly suspected before, specifically, that substituting an amplifiable DNA marker for Rhodamine (a non amplifiable marker) will result in a more sensitive detection assay. It is well known in the art that t it would be advantageous to substitute DNA markers for Rhodamine markers in order to exploit the amplification properties of DNA and improve the sensitivity of any detection assay which employs DNA markers, as evidenced by Wu. While, Applicants' work provides evidence to this effect, the work was not inventive in nature. The instant claims are obvious in view of Singh and Wu and the rejection is proper.

Applicants then argue recognition or appreciation of the detection improvement and that the 1000 fold improvement applied to Singh is not on the order of subattomolar as claimed. This argument is not persuasive because the teaching in Wu of a 1000 fold improvement is enough motivation to combine the references. If the method of Singh is 109 and combining it with Wu will achieve 1012 then an skilled artisan *would be* motivated to combine in order to achieve the improvement. There is no requirement in 103 (a) that the improvement meet a minimum requirement for it to be a motivating improvement.

Applicants argue the Office has based obviousness on the reference merely demonstrating that each of its elements was independently known in the art. This argument is not persuasive because as discussed above reasoning is provided as to why the instant claims are obvious over Singh and Wu. Additionally, Applicants assert for obviousness there is a requirement for a showing of a design need or market pressure to solve a problem and a finite number of predictable solutions. This is not the standard for obviousness.

Finally, Applicants argue secondary considerations as indicated by exhibits 1-6, submitted January 2, 2007. These exhibits do not overcome the obviousness rejections. Applicant seems to argue long-felt need. These exhibits do not demonstrate a long-felt need in the field. This argument is not persuasive because MPEP 716.04 states Establishing long-felt need requires objective evidence that an art recognized problem existed in the art for a long period of time without solution. The relevance of long-felt need and the failure of others to the issue of obviousness depends on several factors. First, the need must have been a persistent one that was recognized by those of ordinary skill in the art. Second, the long-felt need must not have been satisfied by another before the invention by applicant. Third, the invention must in fact satisfy the long-felt need. Applicants' exhibits fail to provide evidence that the need has been a persistent one.

Summary

8. No claims were allowable.

Correspondence

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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Heather Calamita 09/26/2007
Art Unit 1637